

LETTER TO THE EDITOR**TO THE EDITOR****Cerebral Perfusion Pressure Targets in Traumatic Brain Injury: The “Fuzzy” Spots Above Optimal Cerebral Perfusion Pressure**

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The recent publication by Thiara et al¹ in this journal was read with great interest. The authors of this piece should be applauded for the novel approach and important findings in the assessment of the interaction between high cerebral perfusion pressure (CPP) and the development of acute respiratory distress syndrome (ARDS). This particular association has been the subject of great debate in the management of critically ill traumatic brain injury (TBI) patients for years, leading to changes in the recommendations for the upper limit of CPP targets in the Brain Trauma Foundation (BTF) guidelines in an attempt to avoid complicating care through the development of ARDS.² This ARDS risk has been based on retrospective data sets implicating higher CPP values to be associated with this particular complication.

The current suggested upper limits of CPP targets from the BTF guidelines indicate that CPP above 70 mmHg should be avoided.² However, as we make the transition throughout medicine toward individualized therapies and precision targets, such blanket “one size fits all” CPP target ranges in TBI care are likely to be questioned. In particular, with the development of continuous assessment of cerebral autoregulation/cerebrovascular reactivity in TBI, we have the ability to determine individualized CPP values associated with the “optimal” autoregulatory state.^{3,4} It has been well documented that with TBI comes the development of impaired cerebral autoregulation, leading to disruption in maintenance of cerebral blood flow (CBF) regulation.⁵ Furthermore, through experimental studies it is clear that during sustained increases in intra-cranial pressure (ICP), the lower limit of autoregulation (LLA) is shifted to higher mean arterial pressure (MAP) (or CPP) values,⁶ and the upper limit of autoregulation (ULA) is shifted to lower MAP (or CPP) values,⁷ narrowing the classic Lassen plateau⁸ in CBF seen during normal states across the wide range of MAP (i.e., 50–150 mmHg). This exposes the brain to both hypoperfusion and hyperperfusion states, with loss of the classic Lassen response between MAP and CBF.⁸

Various methods have been developed to measure cerebral autoregulation, with current favor shifting toward more continuous methods during the intensive care unit (ICU) phase of care using existing standard monitoring devices. Pressure reactivity index (PRx), the moving correlation coefficient between slow-wave (i.e., vasogenic) fluctuations in ICP and MAP, has become the most widely quoted method, with various other continuous indices derived through invasive/non-invasive monitoring modalities available.⁵ In general, negative values of PRx indicate “preserved” autoregulation, whereas positive values indicate “impaired” autoregulation, with various thresholds associated with clinical outcome published to date. PRx has been

validated as a measure of the LLA in experimental models of both arterial hypotension and sustained intra-cranial hypertension.^{9,10} However, the same cannot be said for the ULA, with a lack of literature to date indicating that any of these continuous vascular reactivity measures, including PRx, can detect the ULA.

By plotting CPP versus PRx over a window of time, via various published algorithms, the parabolic relationship between these two physiologic measures can be demonstrated, with the minimum of the curve indicating the CPP value at which PRx is the most negative (i.e., the “most intact” autoregulation during that period of monitoring). The CPP value is referred to as CPP Optimum (CPPopt).^{3,11} Various studies have been published documenting the strong association between time spent below CPP optimum and the association with poor global outcome.⁴ Such results have sparked interest in this individualized physiologic target in TBI, and have led to the currently ongoing phase II CPPopt study in TBI.

However, the consequence of having CPP above and beyond CPPopt is not as clear. The initial works into CPPopt had difficulties in demonstrating the strong association between CPP values above CPPopt and global outcome.^{3,11} As such, the outcome dichotomization methods were altered to detect a signal for the association between CPPopt and patient outcome, demonstrating the CPP above CPPopt displayed some association with severe disability at 6 months post TBI.³ This lack of strong association between CPP values above CPPopt and outcome has been replicated in various studies on the subject in TBI, with conflicting results.⁴ Thus, from this, it has been unclear as to the significance of having CPP above CPPopt in TBI. The lack of strong reproducible associations of CPP values above CPPopt with global patient outcome likely stems from ongoing ICP-directed therapies received by these patient populations. In the realm of modern ICU management of the TBI patient, ICP therapies are one of the main cornerstones. Thus, it is unlikely to have patients with sustained critically elevated ICP levels during the ICU stay. We know that the ULA in healthy populations is likely to be at a MAP of ~150 mmHg, and is only shifted to lower MAP (or CPP) values with sustained ICP elevations.⁷ Therefore, for the majority of patients with ongoing ICP-directed therapy, it is unlikely that the ULA is shifted to low enough values to have CPP cross above the ULA, exposing the patient to the hyperperfusion/hyperemia-related consequences above that threshold. A similar issue is not seen with the LLA, as MAP and CPP can drift toward and below the LLA during routine TBI care.

The recent publication from Thiara et al in the journal,¹ though demonstrating that CPP values above CPPopt are not associated with ARDS in a retrospective TBI population, it has potentially added to the “fuzzy” nature of the consequence of having CPP values above CPPopt in TBI. The lack of association between CPP values above CPPopt and ARDS is not that surprising, as these calculated CPPopt values are in relation with cerebral autoregulation, not cardiopulmonary physiologic thresholds. This is not to distract from the important results from this study, as it has demonstrated some degree of safety with CPP values above CPPopt, a critical finding for ongoing prospective application of these individualized CPP targets in TBI.

Much further work is required to understand the consequences of maintaining CPP above CPPopt in TBI, as the current literature leaves us with these “fuzzy” areas.

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STATEMENT OF AUTHORSHIP

FAZ is responsible for everything related to this piece of work.

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